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|---|---|
| BRUSCA, JOHN S | |
| **ART UNIT** | **PAPER NUMBER** |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/706,243 | Applicant(s) COX ET AL. | |
|---|---|---|---|
| | Examiner John S Brusca | Art Unit 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *118-183* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *118-183* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) /
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Specification*

1. The objection to the specification in the Office action mailed 17 December 2001 is withdrawn in view of the amendment filed 23 April 2002.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 118-183 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using zinc finger proteins with a single regulatory domain and methods of delivery of zinc finger proteins to cells by introduction of an expression vector, does not reasonably provide enablement for methods of using zinc finger proteins with two regulatory domains and methods of delivery of zinc finger proteins to cells by introduction of exogenous zinc finger proteins to cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must use a zinc finger protein with two regulatory domains and regulate endogenous gene expression by delivery of a zinc finger protein to a cell. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The specification presents guidance in example 3, page 65 through example 7, page 75 to use zinc finger proteins with a single regulatory domain which has the desired regulatory effect, as exemplified by the mutually exclusive use of KRAB or VP16 domains. The specification does not give specific guidance to deliver zinc finger proteins to cells and cause modulation of expression of an endogenous gene.

c) The specification provides working examples only of the use of zinc finger proteins with a desired single regulatory domain, as discussed above. The specification does not provide working examples of delivery of zinc finger proteins to cells to cause modulation of expression of an endogenous gene.

d) The nature of the invention, regulation of gene expression by zinc finger proteins, is complex.

e) A search of the prior art does not show use of zinc finger proteins with two different regulatory domains, or regulation of gene expression by delivery of zinc finger proteins to cells by any direct method. Liu et al. '96 shows use of zinc finger proteins with a single regulatory

domain to regulate endogenous gene expression by delivery of expression vectors that encode the zinc finger protein to cells.

f) The skill of those in the art of molecular biology is high.

g) The prior art does not address the predictability of the full scope of the claimed invention.

h) The claims are broad in that they read on (and in claims 1236, 125, 136, 146, 148, 168, 170, and 179 specifically claim) embodiments that are not supported by the instant specification or the prior art.

In order to practice the claimed invention, the skilled practitioner would first turn to the teachings of the instant specification to practice embodiments of the claimed invention in which zinc finger proteins contain multiple regulatory domains and are delivered as protein to cells. However, the instant specification does not provide specific guidance or working examples of such embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art also does not provide such guidance. Finally, said practitioner would turn to trial and error experimentation to practice the full scope of the claimed invention without guidance from the specification or the prior art. Such represents undue experimentation.

4. Applicant's arguments filed 23 April 2002 have been fully considered but they are not persuasive. The applicants point to description of multiple regulatory domains on a zinc finger protein in the specification, but fail to provide convincing evidence that the combination of the specification and the prior art show how to use a zinc finger with multiple regulatory domains. The applicants point to prior art teachings that domains of choice may be fused to a polypeptide, and it is conceded that one of skill in the art could make zinc finger fusion proteins linked to

multiple regulatory domains. Convincing evidence has not been provided that one of skill in the art could use the claimed invention. Regarding delivery of proteins to cells directly rather than by use of expression vectors, convincing evidence for enablement of the claimed invention by use of direct protein delivery methods that results in significant modulation of gene expression has not been provided.

5. The rejection of claims 119-125, 135, 142-148, 158, 164-170, and 178 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 17 December 2001 has been withdrawn in view of the amendment and arguments filed 23 April 2002.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000).

The claims are drawn to a method of modulating transcription of an endogenous cellular gene comprising contacting the endogenous gene within a living cell with an engineered zinc finger protein that binds a target site in the endogenous gene with a $K_d$ of less than 25 nM and functions to modulate expression of the endogenous gene. In some the expression of the gene is activated by at least 150% or inhibited by at least 20%, the zinc finger proteins are fusion

proteins comprising a regulatory domain or the zinc finger proteins comprise six fingers. In additional embodiments, the cell is a human cell, and the zinc finger protein is expressed from a vector.

Liu et al. '96 shows an assay to determine whether expression by a vector of an unmodified zinc finger protein (EGR-1) can enhance expression of the endogenous tumor growth factor-β1 (TGF-β1) gene. Liu et al. '96 uses human fibrosarcoma HT1080 cells. Figure 1 shows the results of the assay which establishes that EGR-1 increases expression of TGF-β1 and causes reduced cell proliferation.

Choo et al. summarizes on page 9 methods to design a zinc finger protein that binds any desired target site, and further summarizes on page12 that designed zinc finger proteins may be used to alter expression of a desired target gene. Choo et al. shows in example 3, pages 40-47 the use of a vector that expresses an engineered zinc finger protein gene to induce expression of a reporter gene whose promoter comprises a target sequence isolated from a BCR-Abl fusion oncogene (see figure 9). Choo et al. further shows evidence for regulation of chromosomal BCR-Abl fusion oncogenes by transfected engineered zinc finger protein genes on pages 44-47 and in Figure 12. Expression of the zinc finger protein gene affected viability in the absence of IL-3, as shown on page 46 and figure 11. Choo et al. shows on pages 48-51 the design of an engineered zinc finger protein gene that binds the human G12U mutant ras gene.

Liu et al. '97 shows a method of designing a six finger zinc finger protein that binds 18 bp of a target DNA, resulting in engineered zinc finger proteins of high specificity. Liu et al. "97 shows in Table 1 that their method produces zinc finger proteins with $K_d$ levels of as low as

0.46 nM. Liu et al. '97 shows induction and repression by expression of engineered zinc finger proteins fused to regulatory domains in human HeLa cells in figure 4.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the naturally occurring zinc finger protein of Liu et al. '96 by modifying the sequence of the zinc finger protein to bind and regulate the expression of other endogenous genes by use of the methods of Choo et al. and Liu et al. '97 because Choo et al. shows methods for making engineered zinc finger proteins that bind a desired DNA sequence, and further shows that endogenous genes can be regulated by engineered zinc finger proteins, and because Liu et al. '97 shows methods for making engineered zinc finger proteins of high specificity and affinity that can increase or decrease expression of a targeted gene.

10. Claims 139, 161, and 182 are rejected under 35 U.S.C. 103(a) as being unpatentable over, Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000).

The claims are drawn to a method of modulation of expression of an endogenous cellular gene by use of a zinc finger protein wherein the zinc finger protein comprises an SP1 backbone.

Berg reviews the properties of the transcription factor SP1, and shows that SP1 is a $Cys_2His_2$ zinc finger protein. Berg further shows that the amino acid sequence in the zinc fingers controls the binding specificity of such zinc finger proteins.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of modulating gene expression Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above by using SP1 as a starting zinc finger protein because Berg discusses the structural features of SP1 that control specificity of binding to target genes.

11. Claims 131, 132, 154, 155, 175, and 176are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above, and further in view of Berg as applied to claims 139, 161, and 182 above and further in view of Mukhopadhyay et al.

The claims are drawn to a method of modulation of expression of an endogenous cellular gene by use of a zinc finger protein wherein the cellular gene is VEGF.

Mukhopadhyay et al. show in the introduction on page 5629 that VEGF is overexpressed in von Hippel-Lindau disease, and that VEGF expression is regulated by SP1. Mukhopadhyay et al. further shows the binding site of SP1 is at the VEGF enhancer in pages 5631-5634.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the expression of the VEGF gene by use of the engineered SP1

zinc finger protein of Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000) as applied to claims 139, 161, and 182 above because the method would allow for the regulation of expression of VEGF as shown in Mukhopadhyay et al. which would allow for further study of the pathology of von Hippel-Lindau disease.

12. Claims 140, 162, and 183 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. '96 (newly cited) in view of Choo et al. (WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000) as applied to claims 139, 161, and 182 above, and further in view of Jones et al. (newly cited).

The claims are drawn to a method of modulating expression of an endogenous cellular gene by use of a humanized zinc finger protein with an SP1 backbone.

Jones et al. provides guidance throughout to humanize proteins to minimize recognition by the human host immune system when proteins are used in humans therapeutically. Jones exemplifies humanization of an antibody protein.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. '96 (newly cited) in view of Choo et al.

(WO 96/06166, reference BZ in the Form PTO 1449 received 03 November 2000) in view of Liu et al '97 (reference AM in the Form PTO 1449 received 03 November 2000) as applied to claims 118, 122, 126-130, 133, 134, 137, 138, 141, 145, 149-153, 156, 157, 159, 160, 163, 167, 171-174, 177, 180, and 181 above and further in view of Berg (reference CJ in the Form PTO 1449 received 03 November 2000) as applied to claims 139, 161, and 182 above by use of the humanized proteins of Jones et al. for the purpose of facilitating use of the zinc finger proteins in humans without elicitation of an immune response.

13. Applicant's arguments filed 23 April 2002 have been fully considered but they are not persuasive. The applicants argue that Liu et al. '96 does not show modulation of expression of an endogenous gene, or binding of a zinc finger protein to a target site, however Liu et al. '96 shows in the abstract that EGR-1 binds to the TGF-beta1 target gene promoter. The introduction of Liu et al. '96 establishes that EGR-1 is a zinc finger protein. Figure 1 of Liu et al. '96 shows regulation of expression of an endogenous TGF-beta1 gene in cells expressing an exogenous EGR-1 gene.

***Double Patenting***

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 118-135, 137-178, and 180-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037.

The claims are drawn to a method of modulating transcription of an endogenous cellular gene comprising contacting the endogenous gene within a living cell with an engineered zinc finger protein that binds a target site in the endogenous gene with a $K_d$ of less than 25 nM and functions to modulate expression of the endogenous gene.

Claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037 are drawn to a method of modulating transcription of an endogenous cellular gene comprising contacting the endogenous gene within a living cell with an expression vector encoding an engineered zinc finger protein that binds a target site in the endogenous gene with a $K_d$ of less than 25 nM and functions to modulate expression of the endogenous gene.

Claims 89-107, 113, 114, 116-129, 131-136, 142, 143, 145-163, 169, 170, 172, and 173 of copending Application No. 09/229037 represent a species of the instant claimed genus of delivery method of a zinc finger protein to a target cell, and thus anticipates the claimed invention.

This is a provisional obviousness-type double patenting rejection.

16. Applicant's arguments filed 23 April 2002 have been fully considered but they are not persuasive. The applicants state that a restriction requirement in parent application No. 09/229037 serves to make the above double patenting rejection improper. However, the instant and copending claims are both drawn to the same group of a method of using an expression vector to modulate expression of a target gene in a cell. The instant claims are generic as to the method of introduction of the zinc finger protein, and the claims of copending application No. 09/229037 are drawn to the species of introduction by transfection of an expression vector. Since it is well established that species anticipate a genus, the rejection is proper.

17. Claims 141-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30, 31, 33-46, 48-62, and 91-93 of copending Application No. 09/478681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims have limitations of regulation of developmentally silenced genes and other limitations which represent species of the instant generic claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 118-183 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, 22-50, 52-78, and 80-88 of copending Application No. 09/897844. Although the conflicting claims are not identical, they are not patentably distinct from each other because the differences between the claims are minor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 703 308-4231. The examiner can normally be reached on M_F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703 308-4025. The fax phone numbers for the organization where this application or proceeding is assigned are 703 746-5137 for regular communications and 703 746-5137 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

John S. Brusca

Primary Examiner

Art Unit 1631

jsb

July 20, 2002